# Impact of $^{18}$F-Labeled Fluorodeoxyglucose Positron Emission Tomography-Computed Tomography Versus Conventional Staging in Patients With Locally Advanced Breast Cancer

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DOI https://doi.org/10.1200/JCO.23.00249

## ABSTRACT

**PURPOSE** Patients with locally advanced breast cancer (LABC) typically undergo staging tests at presentation. If staging does not detect metastases, treatment consists of curative intent combined modality therapy (neoadjuvant chemotherapy, surgery, and regional radiation). Positron emission tomography-computed tomography (PET-CT) may detect more asymptomatic distant metastases, but the evidence is based on uncontrolled studies.

**METHODS** For inclusion, patients had histological evidence of invasive ductal carcinoma of the breast and TNM stage III or IIb (T3N0, but not T2N1). Consenting patients from six regional cancer centers in Ontario were randomly assigned to $^{18}$F-labeled fluorodeoxyglucose PET-CT or conventional staging (bone scan, CT of the chest/abdomen and pelvis). The primary end point was upstaging to stage IV. A key secondary outcome was receiving curative intent combined modality therapy (ClinicalTrials.gov identifier: NCT02751710).

**RESULTS** Between December 2016 and April 2022, 184 patients were randomly assigned to whole-body PET-CT and 185 patients to conventional staging. Forty-three (23%) PET-CT patients were upstaged to stage IV compared with 21 (11%) conventional staged patients (absolute difference, 12.3%; 95% CI, 3.9 to 19.9; $P$ = .002). Consequently, treatment was changed in 35 (81.3%) of 43 upstaged PET-CT patients and 20 (95.2%) of the 21 upstaged conventional patients. Subsequently, 149 (81%) patients in the PET-CT group received combined modality treatment versus 165 (89.2%) patients in the conventional staging group (absolute difference, 8.2%; 95% CI, 0.1 to 15.4; $P$ = .03).

**CONCLUSION** In patients with LABC, PET-CT detected more distant metastases than conventional staging, and fewer PET-CT patients received combined modality therapy. Our randomized trial demonstrates the utility of the PET-CT staging strategy.

ACCOMPANYING CONTENT

Appendix

Protocol

Accepted April 25, 2023

Published May 26, 2023

J Clin Oncol 00: 1-8



View Online Article

## INTRODUCTION

Patients with locally advanced breast cancer (LABC) present clinically with large tumors in the breast that can involve the chest wall or skin, clinically fixed axillary lymph nodes, or infraclavicular, supraclavicular, or internal mammary lymphadenopathy.[1] They are at significant risk of metastatic disease and typically undergo pretreatment staging tests.[2] The extent of disease guides the decision on intent and mode of therapy. If staging does not detect metastases, the patient undergoes combined modality therapy of curative intent consisting of neoadjuvant systemic therapy and surgery, followed by regional radiation therapy.[3,4] If metastases are present, the prognosis is different and the recommended plan for combined therapy usually changes to less aggressive strategies to control the disease.[5]

Traditionally, staging of LABC is performed using anatomic-based imaging methods such as chest radiograph, liver ultrasound, or computed tomography (CT) for lung and liver metastases and bone scintigraphy for skeletal metastases. There have been reports suggesting that $^{18}$F-labeled

## CONTEXT

**Key Objective**

In patients with locally advanced breast cancer, does staging with positron emission tomography-computed tomography (PET-CT) detect more distant metastases than conventional staging (bone scan, CT of the chest/abdomen and pelvis)? To our knowledge, our trial is the first and only randomized controlled trial on this subject.

**Knowledge Generated**

More than twice as many PET-CT patients were upstaged to stage IV than conventionally staged patients. Fewer PET-CT patients received combined modality therapy (neoadjuvant chemotherapy, surgery, and radiotherapy) of curative intent.

**Relevance *(K.D. Miller)***

PET/CT staging identifies distant disease in more patients and changes goals of therapy. Further research is needed to determine the impact on patient outcome.*

*Relevance section written by *JCO* Senior Deputy Editor Kathy D. Miller, MD.

fluorodeoxyglucose ($^{18}$F-FDG) positive emission tomography-CT (PET-CT) may be of value in the detection of asymptomatic distant metastases compared with other imaging tests in women with newly diagnosed breast cancer, and the detection rate increases with stage.[6-10] These studies were often relatively small, retrospective, and uncontrolled. They contained heterogeneous patient populations with differing baseline recurrence risks and varied in the types of conventional imaging tests used for comparison.[6-10] Most studies did not describe the clinical utility of the test, that is, whether it changed clinical management.[11,12]

The Ontario Clinical Oncology Group (OCOG) has conducted a series of trials to provide evidence on the utility of PET-CT in oncology.[13-19] The results have informed funding decisions in Ontario, Canada.[20] We report the results of an OCOG randomized trial comparing $^{18}$F-FDG PET-CT with conventional staging in patients with LABC. We hypothesized that in such patients, staging with PET-CT would identify more patients with metastatic breast cancer (stage IV) compared with staging with conventional tests and that the upstaging of patients would affect clinical management decisions, for example, avoidance of multimodality therapy of curative intent.

## METHODS

### Patients

For inclusion in this study, patients had histological evidence of invasive ductal carcinoma of the breast and stage III by TNM (T0N2, T1N2, T2N2, T3N1,2 or T4) or IIb breast cancer (T3N0)[21] on the basis of clinical information (physical examination, imaging) and were being considered for combined modality therapy (chemotherapy, surgical resection, and radiotherapy) of curative intent.[4] Patients with T2N1 (also stage II) tumors and patients not undergoing neoadjuvant treatment were excluded. The exclusion criteria are listed in Appendix Table A1 (online only). Because of concerns regarding lower $^{18}$F-FDG avidity of lobular breast cancer, those patients were followed through a separate, concurrent cohort study which was run in parallel; the results will be published separately. Patients with mixed histology (ductal and lobular) were eligible for the current trial.

Patients were recruited at six regional cancer centers in Ontario: Juravinski Cancer Centre—Hamilton Health Sciences, London Health Sciences Regional Cancer Centre, University Health Network Princess Margaret Cancer Centre, Ottawa Hospital Cancer Centre, Sunnybrook Health Sciences-Odette Cancer Centre, and the Thunder Bay Regional Health Sciences Cancer Centre. The PET-CT scanners were located at six academic institutions associated with the cancer centers. To ensure adherence to standard operating procedures, all participating sites were accredited by a Provincial Quality Assurance Program which included a qualifying PET scan report using the Standard NEMA IEC Body Phantom Set (ClinicalTrials.gov identifier: NCT02751710).

### Study Procedures

#### *Random Assignment*

The Ontario Cancer Research Ethics Board provided ethics approval, and written informed consent was obtained from all patients. Study enrollment and random assignment were coordinated centrally by OCOG in Hamilton, ON. Initial assessments were performed, including physical examination and cancer staging at study sites. After confirmation of patient eligibility and documentation of written informed consent, the clinical center accessed OCOG's web-based interactive registration/random assignment system. Eligible consenting patients were randomly allocated (1:1) to whole-body $^{18}$F-FDG PET-CT alone or conventional breast cancer staging consisting of a bone scan and CT imaging with contrast of the chest/abdomen and pelvis. Random

assignment was stratified by the presence or absence of inflammatory breast cancer (stage T4d) and clinical center.

### *Interventions*

Patients in the experimental arm underwent whole-body $^{18}$F-FDG PET-CT as the sole modality of staging. PET-CT was to be performed within 2 weeks (±7 days) of random assignment. Fasting blood glucose level was required to be <9.7 mmol/L before injection of $^{18}$F-FDG. The imaging procedure commenced approximately 60 minutes after administration of $^{18}$F-FDG at a dose of 5MBq/kg of body weight (±10%) to a maximum of 500 MBq, with a low-dose CT scan from the skull base to the upper thighs to enable definition of the axial field of view and for use in attenuation correction of the emission scan. This was followed by acquisition of the $^{18}$F-FDG emission scan. In cases where PET-CT was equivocal, further imaging (with or without biopsy) was recommended.

PET-CT was initially interpreted by a nuclear medicine physician at the study site. The images were also uploaded to a central server in the Quantitative Imaging for Personalized Cancer Medicine Program at University Health Network, Toronto. An independent central read was performed by a second nuclear medicine physician not from the study site and uploaded to a central database. Any major discrepancies were resolved by consensus. Each focus of $^{18}$F-FDG uptake on the PET-CT scan was interpreted using a four-point ordinal scale with 1—negative, 2—equivocal, 3—probably positive, and 4—positive. Refer Appendix Table A2 (online only) for PET-CT interpretation criteria. Categories 3 and 4 were considered positive for the presence of cancer. Measurement of maximum standard uptake value normalized to body mass was obtained from all primary breast cancers and metastases.

Patients in the control arm underwent conventional staging consisting of a bone scan and CT with contrast of the chest/abdomen and pelvis to include visualization of the lungs, liver, adrenal glands, and pelvis. These tests were to be performed within 2 weeks (±7 days) of random assignment. In cases where bone scan or CT were equivocal, further imaging with or without biopsy was recommended. Experienced nuclear medicine physicians and radiologists read bone scans and CT scans, respectively, in participating academic centers. There was no formal quality assurance process for performance and interpretation of bone scans and CT scans.

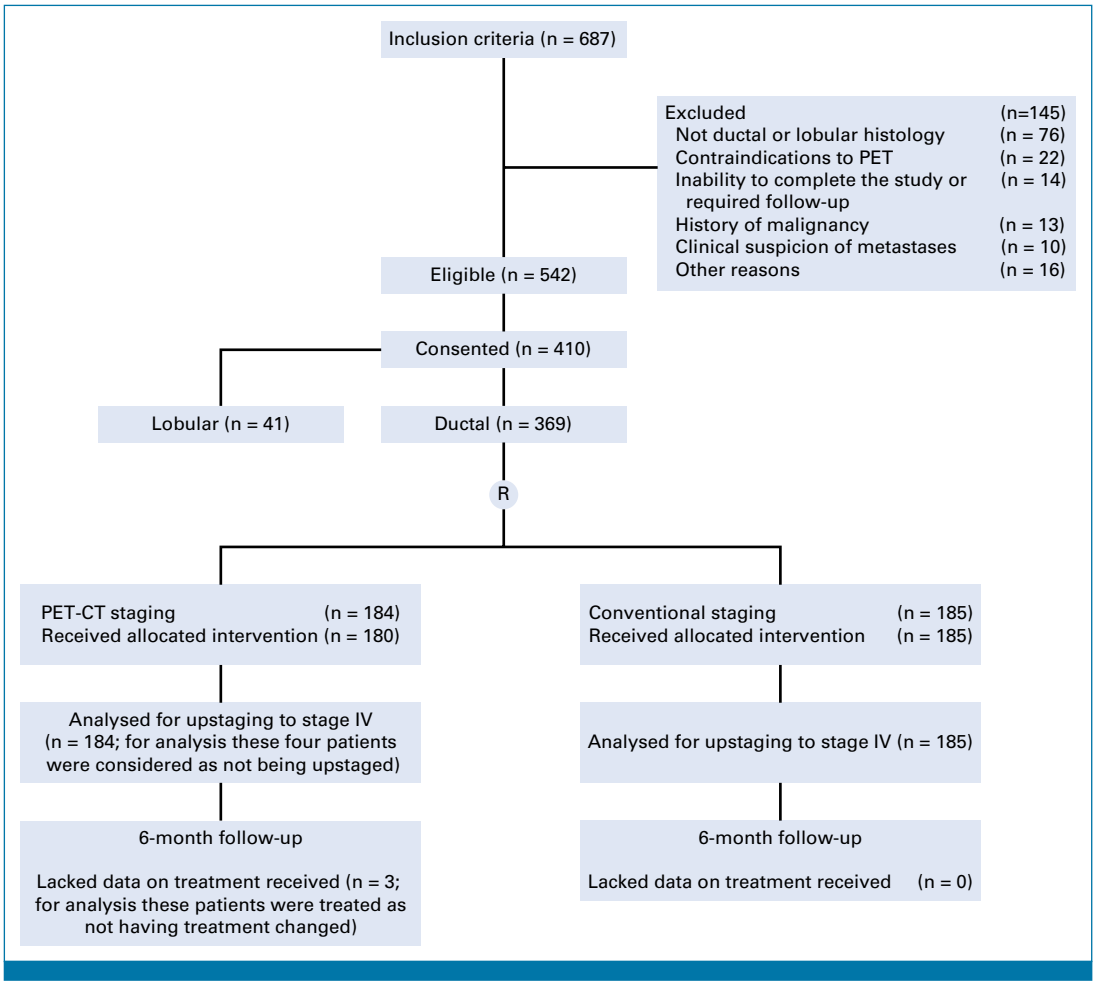


**FIG 1.** CONSORT diagram. PET-CT, positron emission tomography-computed tomography.

**TABLE 1.** Baseline Characteristics

| Characteristic | PET-CT (n = 184) | Conventional (n = 185) |
|---|---|---|
| ECOG, No. (%) | | |
| 0 | 165 (90) | 166 (90) |
| 1 | 15 (8) | 17 (9) |
| 2 | 1 (<1) | 1 (<1) |
| Missing | 3 (2) | 1 (<1) |
| Stage, No. (%) | | |
| IIB | 52 (28) | 42 (23) |
| IIIA | 93 (50) | 104 (56) |
| IIIB | 36 (20) | 35 (19) |
| IIIC | 3 (2) | 4 (2) |
| Grade, No. (%) | | |
| I | 7 (4) | 5 (3) |
| II | 88 (48) | 86 (46) |
| III | 76 (41) | 86 (46) |
| Unknown | 13 (7) | 8 (4) |
| ER status, No. (%) | | |
| Positive | 129 (70) | 132 (72) |
| Negative | 55 (30) | 52 (28) |
| PR status, No. (%) | | |
| Positive | 96 (52) | 99 (54) |
| Negative | 87 (47) | 84 (45) |
| Unknown | 1 (<1) | 2 (1) |
| Her2Neu, No. (%) | | |
| Positive | 65 (35) | 58 (32) |
| Negative | 119 (65) | 120 (65) |
| Missing | 0 (0) | 7 (3) |
| Age, years: mean, SD | 53 (13) | 53 (13) |
| Primary tumor size, cm: mean, SD | 6.6 (2.7) | 7.0 (3.5) |

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; Her2Neu, human epidermal growth factor receptor 2; PET-CT, positron emission tomography-computed tomography; PR, progesterone receptor; SD, standard deviation.

**TABLE 2.** Proportion Upstaged to Stage IV

| Strata | Upstaged | PET-CT, n (%) | Conventional, n (%) |
|---|---|---|---|
| Inflammatory present | | 16 | 17 |
| | Yes | 4 (25) | 4 (24) |
| | No | 12 (75) | 13 (76) |
| Inflammatory absent | | 168 | 168 |
| | Yes | 39 (23) | 17 (10) |
| | No | 129 (77) | 151 (90) |
| Combined | | 184 | 185 |
| | Yes | 43 (23) | 21 (11) |
| | No | 141 (77) | 162 (89) |

NOTE. Relative risk: PET-CT versus conventional (95% CI), 2.4 (1.4 to 4.2). Absolute difference (95% CI), 12.3 (3.9 to 19.9). $P = .002$ (Cochrane Mantel-Haenszel).
Abbreviation: PET-CT, positron emission tomography-computed tomography.

### *Patient Treatment*

Patients found to have locoregional disease only (ie, negative for upstaging) proceeded to multimodality treatment consisting of preoperative chemotherapy (plus trastuzumab if the tumor was human epidermal growth factor receptor 2–positive), surgery, and radiotherapy. Rarely, neoadjuvant endocrine therapy was administered instead of chemotherapy. The details of these treatments were left to the local investigators. An anthracycline and taxane-containing regimen was suggested for chemotherapy and modified radical mastectomy for surgery. In some cases, sentinel node biopsy and breast conserving surgery could be offered, followed by local regional radiation (breast/chest wall tangents with a matched superior field to include axillary and supraclavicular lymph nodes). At the discretion of the treating radiation oncologist, inclusion of the internal mammary nodes was recommended but not mandatory, pending the lung dose. Endocrine therapy was added for hormone receptor–positive disease. If a patient was found to have metastatic disease, therapy was at the discretion of the local clinical team.

### *Follow-Up*

Patients underwent a follow-up clinical assessment at 6 and 12 months in the first year calculated from the date of study enrollment. Tests performed as a result of staging; details of systemic therapy, surgery, radiation delivered, and pathology results; disease status; and quality-of-life information were captured at 6 and 12 months.

## Outcomes

The primary outcome was upstaging to stage IV after the staging tests. An important secondary outcome was having received multimodal therapy of curative intent.

## Analysis

Descriptive statistics were used to summarize baseline characteristics. The Cochrane Mantel-Haenszel test adjusting for presence or absence of inflammatory breast cancer compared the proportions of patients in each group upstaged to stage IV and the proportions of patients receiving combined modality therapy of curative intent.[22] Center was not adjusted for because of the sparse nature of data within the strata $2 \times 2$ tables. The Fisher exact test compared the proportion of patients in each group with regional nodes positive among those upstaged patients and the proportion of patients who did not receive combined modality treatment. Treatment effects are reported as absolute difference and relative risk with corresponding 95% CI. The number of additional tests is summarized descriptively. Exploratory subgroup analysis to assess the heterogeneity of effects

**TABLE 3.** Sites of Metastases for Upstaged Patients

| Distant Site | PET-CT, No. (n = 184) | Conventional, No. (n = 185) |
|---|---|---|
| Bone only | 14 | 6 |
| Bone, liver | 6 | 1 |
| Bone, lung | 0 | 5 |
| Mediastinal nodes only | 3 | 0 |
| Lung only | 3 | 2 |
| Liver only | 2 | 0 |
| Bone, mediastinal nodes | 2 | 0 |
| Bone, lung, liver | 2 | 2 |
| Bone, lung, mediastinal nodes | 2 | 0 |
| Mediastinal nodes, neck nodes | 1 | 0 |
| Lung, mediastinal nodes | 1 | 0 |
| Lung, mediastinal nodes, contralateral,[a] neck nodes | 1 | 0 |
| Liver, ovary | 1 | 0 |
| Liver, mediastinal nodes | 1 | 0 |
| Lung, liver | 1 | 2 |
| Bone, mediastinal nodes, neck nodes | 1 | 0 |
| Bone, mediastinal nodes, contralateral,[a] pleura | 1 | 0 |
| Bone, mediastinal nodes, retroperitoneal nodes | 1 | 0 |
| Lung, bladder | 0 | 1 |
| Liver, adrenal | 0 | 1 |
| Pancreas | 0 | 1 |

NOTE. Four patients in the PET-CT group did not have a PET scan and withdrew at baseline. To be conservative, these patients were treated as not being upstaged.
Abbreviation: PET-CT, positron emission tomography-computed tomography.
[a]Contralateral axillary node.

among subgroups of patients was performed on stage, presence or absence of inflammatory breast cancer, estrogen receptor status, triple negative, and human epidermal growth factor receptor 2 (Her2Neu) status. Interaction test was done by including a treatment group by subgroup interaction term in a logistic regression model.

### Sample Size

In brief, the expected estimates for detection of metastases for conventional staging and PET-CT were 12% and 24%, respectively. Assuming a two-sided alpha 0.05, power of 80% and allowing for an additional 5% for loss to follow-up and nonadherence, a total of 370 patients were required on the basis of the Fisher exact test.

## RESULTS

Between December 2016 and April 2022, 184 patients were randomly assigned to PET-CT and 185 patients to the conventional staging (Fig 1). The baseline characteristics were similar between the two staging groups (Table 1). Four patients in the PET-CT group did not have a PET scan and withdrew at baseline. To be conservative, these patients were considered as not being upstaged.

Overall, 43 (23%) of PET-CT patients were upstaged to stage IV compared with 21 (11%) conventional staged patients (relative risk, 2.4; 95% CI, 1.4 to 4.2; $P = .002$; Table 2). There were 33 patients with inflammatory breast cancer. Four of 16 (25%) PET-CT patients were upstaged to stage IV compared with 4 of 17 (24%) conventional patients. In the patients without inflammatory breast cancer, 39 of 168 (23%) PET-CT patients were upstaged compared with 17 (10%) of 168 in the conventional group.

The percent agreement between the local reader and central reader was 92%, and kappa was 0.78 (95% CI, 0.68 to 0.88). According to Landis and Koch,[23] this is considered substantial agreement. Of note, there was only one case where the local read was negative for distant metastases, but the central read and the consensus read were positive. On the other hand, there were three cases where the local read was positive for distant metastases and the corresponding central reads were negative, but the consensus reads were all positive.

The sites of distant metastases are shown for each upstaged patient in Table 3. In the PET-CT group, the most common sites were bone (bone only, 14 and bone plus another site, 15), followed by mediastinal nodes (alone, 3 and mediastinum plus other site, 11), liver (alone, 2 and liver plus another site, 4), and lung (alone, 3 and liver plus another site, 7). In the conventional group, bone was the most common site of metastases (bone alone, 6 and bone plus another site, 8). Several patients underwent further testing after they were upstaged, either to confirm the site of metastasis or to serve as a baseline to monitor therapy (Appendix Table A3, online only).

Detecting cancer in regional nodes (eg, axillary, internal mammary, and supraclavicular nodes) was not a criterion for upstaging. In the 184 PET-CT patients, 42 (22.7%) had positive regional nodes on imaging (including 19 patients with internal mammary nodes, 11 with supraclavicular nodes, and 40 with axillary nodes) compared with 13 (7.1%) in the conventional group (all axillary nodes). It is noteworthy that 42 (97.7%) of the 43 PET-CT patients who were upstaged to stage IV had positive regional nodes compared with 13 (61.9%) of the 21 upstaged in the conventional group, $P = .03$.

Post hoc subgroup analyses exploring heterogeneity within tumor factors (baseline stage, estrogen receptor, Her2Neu, and triple negative) and intervention group were performed. Tests of interaction were not statistically significant (Fig 2).

Thirty-five (81.3%) of the 43 PET-CT patients who were upstaged and 20 (95.2%) of 21 conventional patients who were upstaged had treatment changed and did not receive combined modality treatment of curative intent. The

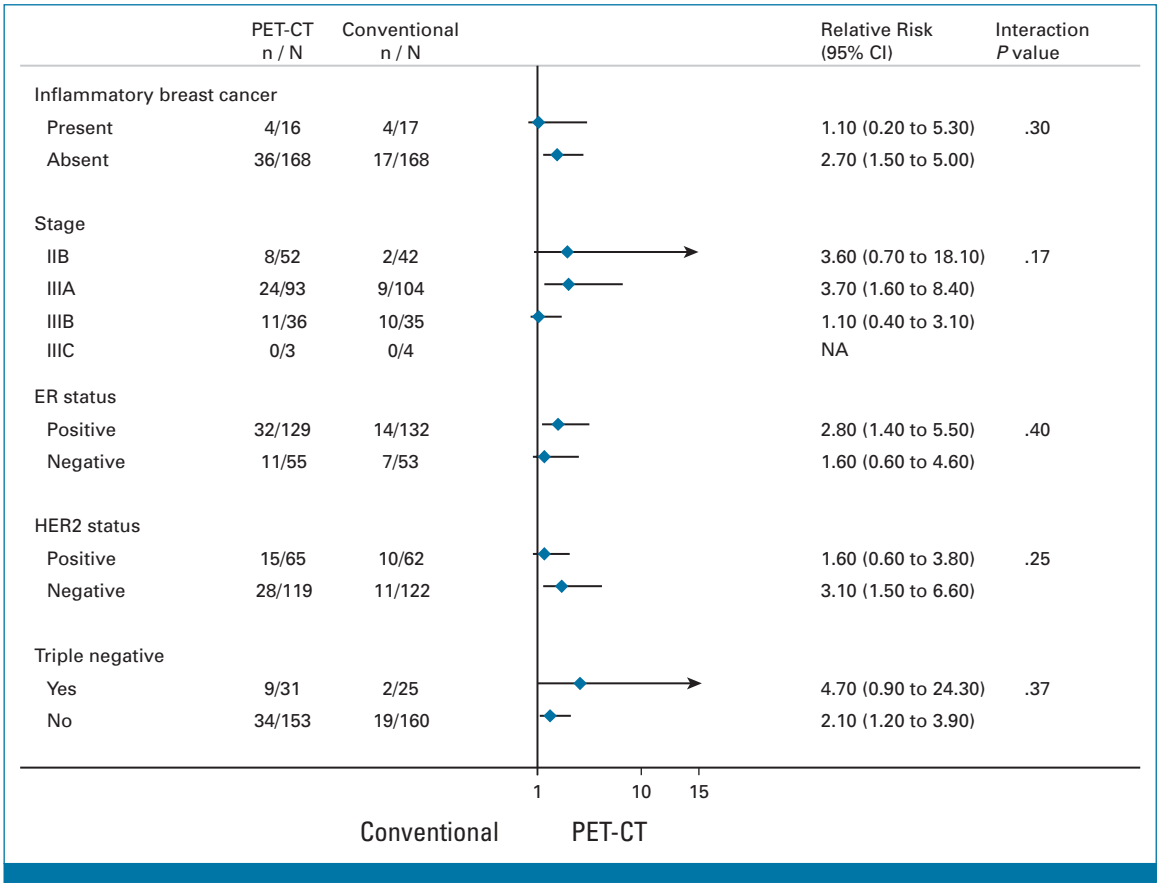


**FIG 2.** Relationship between subgroups and upstaging. ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; NA, not available; PET-CT, positron emission tomography-computed tomography.

treatment received when patients were upstaged is shown in Appendix Table A4 (online only). Thus, 35 of 184 (19%) PET-CT patients did not receive combined modality treatment compared with 20 of 185 (11%) conventional staging patients (absolute difference, 8.2%; 95% CI, 0.1 to 15.4; $P = .03$).

Seven patients in the PET-CT arm died compared with six in the conventional arm.

## DISCUSSION

In women with LABC, staging defines disease extent and guides therapy. When planning our trial, we hypothesized that PET-CT could detect more distant metastases than usual staging with bone scan and CT of the thorax/abdomen and pelvis. The results of our study support this hypothesis. More than twice as many patients were upstaged with PET-CT compared with conventional staging. The implications are that patients who are upstaged to stage IV would avoid the toxicity and adverse impact of aggressive combined modality therapy on quality of life when the disease is incurable. Exploratory subgroup analyses of tumor-related factors were unable to predict upstaging likely because of low power for interactions.

Our second important a priori hypothesis was that upstaging would result in a change in patient management. This is referred to as utility of a test.[11,12] Many of the previous studies on PET-CT in stage III breast cancer did not consider utility.[6-10] In our trial, more than 85% of upstaged patients had their clinical management changed to less aggressive treatments. There was a significant reduction in the proportion of patients in the PET-CT group who received combined modality therapy compared with control patients which supports our second hypothesis.

PET-CT was also more sensitive than conventional staging in identifying regional nodal metastases, especially internal mammary and supraclavicular nodes. In addition, the observation that almost 100% of patients who were upstaged had positive regional nodes provides insight on the spread of breast cancer. Over a century ago, Halstead proposed that breast cancer was a local disease that spread in a stepwise manner from the primary tumor to the regional lymphatics and then systemically to distant organs.[24] This theory gave way to the concept from Fisher that breast cancer is a systemic disease from the beginning and hematogenous dissemination is key.[25] Our results suggest that the former mechanism still plays a role.

It is interesting that treatment did not change in approximately 20% of upstaged PET-CT patients but changed in most upstaged conventional imaging patients. Patient/

oncologist decision making is difficult when early asymptomatic metastases are found. There are clinical situations where the default management could very well have been chemotherapy, for example, inflammatory breast cancer, triple-negative disease, visceral metastases, and very young age. Although systemic therapy was not planned as curative, it is plausible that some of these patients had a complete clinical response to chemotherapy and then had surgery, followed by radiation.[26] In addition, in recent years, the concept of aggressive treatment of oligometastases has influenced treatment.[27] These factors would not explain the observed difference in change in treatment between PET-CT and conventional imaging patients. Perhaps in some cases, the increased nodal metastases, for example, mediastinum and hilar, detected with PET-CT were not considered as serious as other sites of metastases and were not a deterrent for combined modality therapy. Another explanation may be that it is a chance finding on the basis of small numbers.

There can be other noncancerous causes of adenopathy, bone abnormalities, and lung nodules. In our trial, not all patients who were upstaged had confirmatory tests, and most patients did not undergo a biopsy. Thus, the potential for a false-positive PET-CT reading is a limitation.

Our trial did not include patients with earlier stages of breast cancer, for example, stages T1N1 and T2N1. Thus, the results are not generalizable to such patients.

The number of patients who died is relatively low. Any inferences concerning survival results are limited because of the small sample size and short follow-up. The study Protocol specifies that quality-of-life data are collected at 6 and 12 months and survival data at 12 months and 3 and 5 years. With longer follow-up, we hope to be able to explore some of the downstream implications of the upstaging data.

This was not a double-blind trial, and the open design could be a source of bias. We believed that a double-blind design would not be logistically feasible. There were strict objective criteria for upstaging, and all cases were reviewed by an external committee of experienced oncologists not involved in the care of study participants to determine whether upstaging had occurred and whether there had been a change in intended care. The performance of PET-CT was according to a provincial quality assurance program. PET-CT scans were interpreted independently by two readers. This was not done for the conventional testing group, and the dual review of the PET-CT versus the single review is another potential source of bias.

The medical costs of caring for patients with cancer are high and are increasing because of new treatments, new technology, and an aging population.[28] In 2009, an Institute of Medicine report prioritized comparative effectiveness research for PET-CT in staging of patients with cancer patients.[29,30] This approach was endorsed by the American Society of Clinical Oncology.[31] Our clinical trial can be considered as comparative effectiveness research. In France, PET-CT has been adopted for staging of LABC on the basis of uncontrolled studies that evaluated the accuracy of the test in detecting metastases.[32] The National Comprehensive Cancer Network guidelines for breast cancer state that PET-CT is considered optional in circumstances in which other imaging tests are equivocal.[33] This is based on level 2A evidence defined as, based on lower-level evidence there is uniform consensus that the recommendation is appropriate. To our knowledge, our trial is the only randomized trial that addresses the utility of PET-CT for LABC. On the basis of the results, the Ontario Ministry of Health now funds PET-CT for the staging of patients with clinical stage IIb (T3 N0) and stage III breast cancer.


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## EQUAL CONTRIBUTION

I.D. and U.M. contributed equally to this work.

## CLINICAL TRIAL INFORMATION

NCT02751710 (PETABC)

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO.23.00249.

## DATA SHARING STATEMENT

A complete deidentified patient-level data set will be made available to researchers for the purpose of meta-analysis or a newly proposed study. Data will be made available following submission of a maximum two-page proposal by the requestor. The trial Steering Committee will review and, if acceptable, provide approval of the request. A signed data sharing access agreement will be required. The data will be provided as SAS data sets (CPT or XPT file). Any other format requests may incur costs to the requestor. Data will become available 1 year after publication of the initial study results. Data availability will end 4 years after publication of the initial study results. Data requests should be sent to parpia@mcmaster.ca.

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## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

**Impact of $^{18}$F-Labeled Fluorodeoxyglucose Positron Emission Tomography-Computed Tomography Versus Conventional Staging in Patients With Locally Advanced Breast Cancer**

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/authors/author-center.

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No other potential conflicts of interest were reported.

# APPENDIX

**TABLE A1.** Exclusion Criteria

| Criterion |
|---|
| Patients who satisfy any one or more of the following are not eligible for this study: |
| 1. Age younger than 18 years |
| 2. ECOG performance status >3 |
| 3. Previous systemic therapy (eg, neoadjuvant chemotherapy or hormonal therapy) for current breast cancer |
| 4. Previous staging investigations for current breast cancer |
| 5. Breast cancer with primary histological subtypes other than ductal or lobular (note: patients with mixed disease will be eligible for random assignment) |
| 6. Clinical suspicion of metastatic disease |
| 7. Relative contraindications to PET (eg, uncontrolled diabetes [ie, inability to decrease serum glucose below 10.2 mmol/L], claustrophobia, inability to be still for 30 minutes) |
| 8. Inability to lie supine for imaging with PET-CT |
| 9. Inability to undergo CT because of known allergy to contrast |
| 10. History of another invasive malignancy within the previous 2 years (exception of nonmelanoma skin cancer) or a synchronous primary cancer, including a synchronous contralateral breast cancer (note: patients found to have a contralateral breast cancer on study imaging after random assignment will remain in the study) |
| 11. Known pregnancy or lactating female |
| 12. Inability to complete the study or required follow-up |

Abbreviations: ECOG, Eastern Cooperative Oncology Group; PET-CT, positron emission tomography-computed tomography.

**TABLE A2.** PET-CT Interpretation Criteria

| Site | Criteria for Malignancy |
|---|---|
| Regional | |
| Lymph nodes | >1.5 cm with uptake greater than blood pool and <1.5 cm in diameter with uptake greater than background, unless reactive morphology[a] |
| Distant | |
| Bone | Focal uptake in typical location for metastases even without CT correlate, excluding degenerative or post-traumatic findings |
| Lung | Focal $^{18}$F-FDG uptake in a pulmonary nodule |
| Liver | Focal $^{18}$F-FDG uptake above background liver uptake |
| Adrenal | Uptake well above background liver, especially if density on noncontrast CT is >10 HU<br>Diffuse uptake in a morphologically normal adrenal gland should not be considered metastatic |
| Others | Focal $^{18}$F-FDG uptake in thyroid gland are more commonly primary thyroid neoplasms and should not be considered metastatic<br>Focal $^{18}$F-FDG uptake in an ovary often inflammatory after ovulation should be interpreted according to timing of menstrual cycle in relation to the scan |

Abbreviations: AJCC, American Joint Committee on Cancer; $^{18}$F-FDG, $^{18}$F-labeled fluorodeoxyglucose; PET-CT, positron emission tomography-computed tomography.
[a]Node location by AJCC seventh classification.

**TABLE A3.** Diagnostic Tests for Patients Upstaged Within 6 Weeks of Random Assignment

| Diagnostic Test | PET-CT (n = 43) | Conventional (n = 21) |
|---|---|---|
| Patients with diagnostic tests, No. | 22 | 5 |
| Diagnostic tests,[a] No. | 35 | 7 |
| Bone scan | 11 | 0 |
| CT scan | 9 | 0 |
| MRI | 4 | 2 |
| Mediastinoscopy | 1 | 0 |
| Needle aspirate | 1 | 1 |
| US | 4 | 2 |
| X-ray | 5 | 2 |

Abbreviations: MRI, magnetic resonance imaging; PET-CT, positron emission tomography-computed tomography; US, ultrasound.
[a]Patient can have more than one test.

**TABLE A4.** Changes in Treatment

| Treatment[a] | Patient No. |
|---|---|
| Endocrine therapy | 7 |
| Endocrine therapy + CD4/6 inhibitor | 7 |
| Endocrine therapy + CD4/6 + LHRH agonist or oophorectomy | 4 |
| Chemotherapy | 12 |
| Chemotherapy + trastuzumab + pertuzumab | 17 |
| Surgery | 1 |
| Radiation | 3 |
| Bisphosphonate | 9 |

Abbreviation: LHRH, luteinizing hormone-releasing hormone.
[a]Patient can have more than one treatment type.